



# What are the Long-term Effects of PM?

Presenter: Morton Lippmann, PhD

New York University PM Center

## Science Questions

1. What is the magnitude of excess mortality and morbidity attributable to chronic exposure to particulate matter (PM) in ambient community air in terms of:

- regulated indices (PM<sub>2.5</sub> and PM<sub>10-2.5</sub>)
- other airborne concentration indices that may warrant regulation, such as PM<sub>1</sub>, Ultrafine particle number (UFP), specific components and/or source categories (e.g., power plant effluents, motor vehicle exhaust, wood smoke, etc.)
- enhanced risks to susceptible subpopulations (fetuses, young children, elderly, and people with pre-existing chronic diseases such as asthma, COPD, atherosclerosis, diabetes, etc.)

- the co-presence of other environmental risk factors, such as other criteria pollutants, allergenic and infectious agents, cigarette smoke, other indoor pollutants, occupational exposures, and diet.

- temporal patterns of exposure (influence of periodic high peak levels, and early life vs. recent years' exposures)?

2. What are the underlying biological mechanisms by which inhaled PM causes or contributes to disease initiation and progression to morbidity and mortality in terms of:

- cardiovascular disease
- lung cancer
- pulmonary disease
- nervous system disease
- reproductive outcomes
- immune system dysfunction

## Research Goals

1. Determine, through studies of population impacts, the specific influences of PM size fractions, chemical components, and source-related mixtures on human health and welfare.

2. Characterize, through laboratory-based investigations, the components within or on PM surfaces that determine the distribution of particle deposition within the respiratory airways, their clearance and translocation pathways as particles, their metabolic pathways after dissolution, the release of mediators by the cells that they contact or enter, and the sequence of events that lead to measurable health effects.

## Bottom Line

Substantial progress has been made, during the past six years, by EPA scientists, and by those engaged at the PM Centers in research supported by EPA, in addressing the long-term effects of exposures to ambient air PM. The research described in this poster has, collectively, provided new insights and better investigatory tools for further research studies that can more definitively determine the specific disease processes and population impacts resulting from exposures to PM in ambient air, and the PM components and sources responsible for these impacts. An improved understanding of the causal components of PM, and of their sources, is essential to guide control decisions and to inform OMB, the Congress, and the public.

## ADULT COHORTS

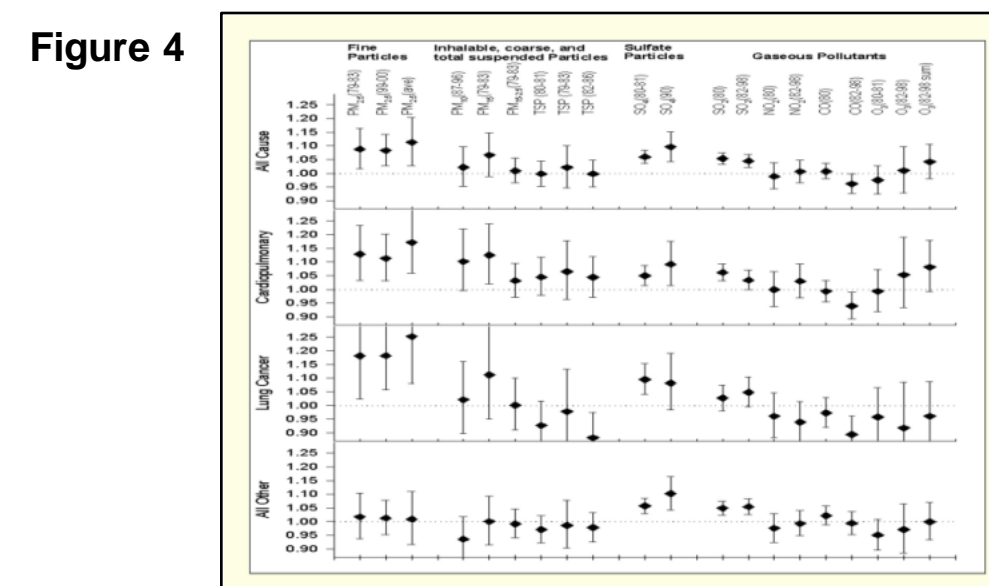
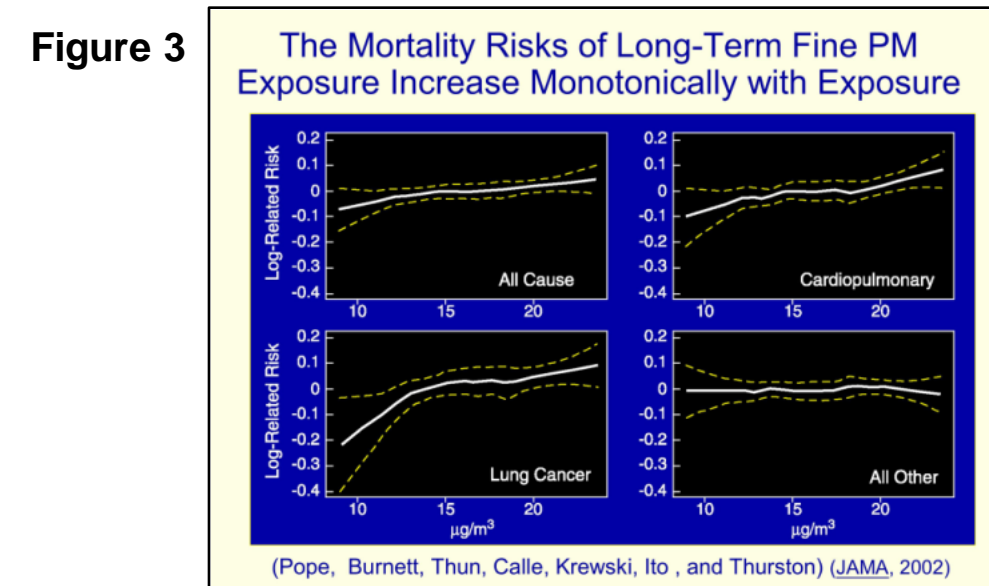
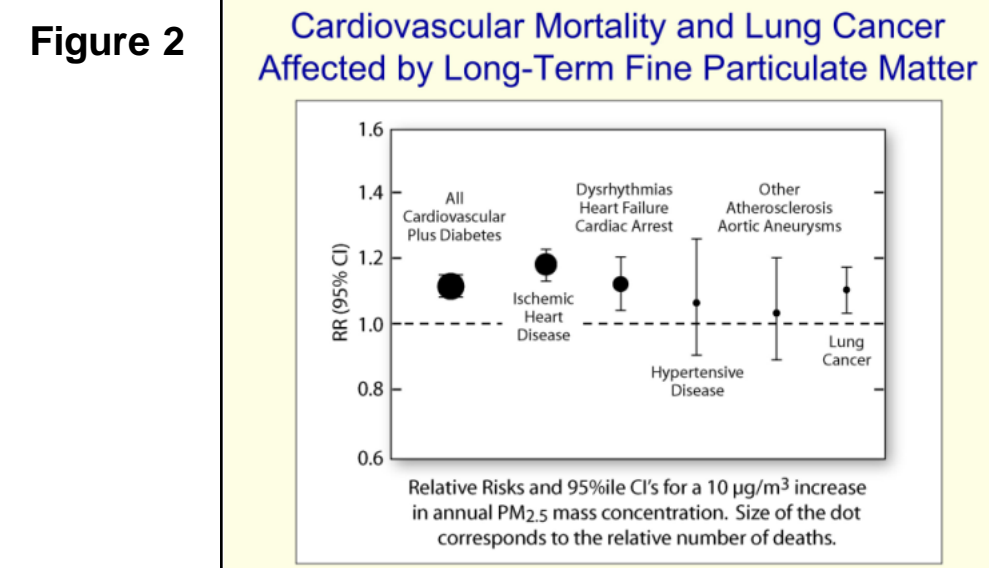
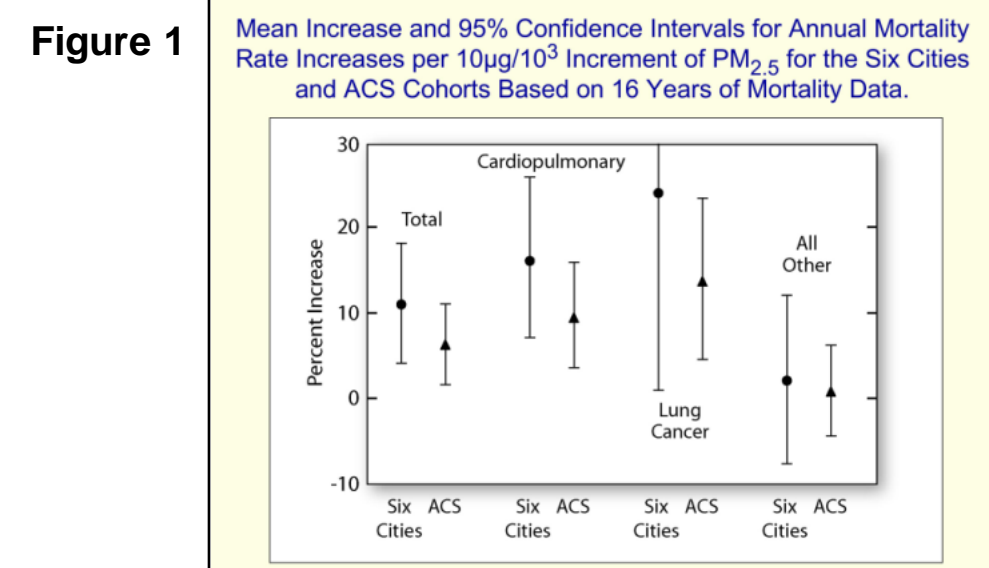
### KNOWLEDGE IN 1997:

Two large cohort mortality studies, i.e., Harvard Six-Cities and American Cancer Society (ACS) linked annual average PM<sub>2.5</sub> with premature total and cardiopulmonary mortality. Also, there was limited evidence linking long-term PM<sub>10</sub> with the development of bronchitis.

### KNOWLEDGE GAINED SINCE 1997:

HEI reanalysis of data from Six-Cities and ACS cohorts confirmed validity of original analyses, and demonstrated that alternate model specifications gave similar results.

Extensions of mortality follow-up from 7 to 16 years in both cohorts confirmed excesses in PM<sub>2.5</sub>-associated total and cardiopulmonary mortality, and demonstrated excess lung cancer mortality (**Figure 1**). For the ACS cohort, most of the excess mortality was shown to be related to cardiac disease (**Figure 2**). These analyses showed no evidence for concentration thresholds (**Figure 3**). For both cohorts, the effects were greatest in those with the lowest educational attainment, which may account for the greater coefficient of response in the Six-Cities cohort, which was a more representative population than the largely well educated ACS cohort (**Figure 1 and Table I**). With the exception of SO<sub>2</sub>, the criteria pollutant gases were not correlated with annual mortality (**Figure 4**). The SO<sub>2</sub> may be serving as a marker for the acidic sulfate particles that form in the atmosphere from SO<sub>2</sub> as a precursor.

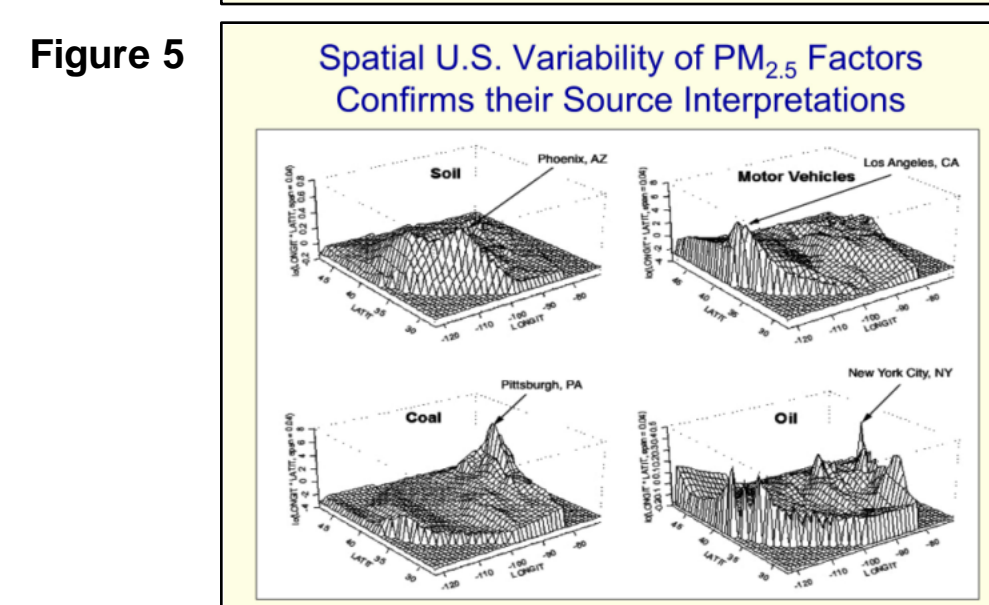


**Table I**

Harvard Six-Cities Study: Adjusted Annual Mortality Rate Ratios and 95% Confidence Intervals for a 10µg/m³ Change in PM<sub>2.5</sub> Estimated from Cox Proportional Hazards Models

Cause	No. Cases	RR (95% CI)	
		Average PM <sub>2.5</sub> <sup>1</sup>	Time-varying PM <sub>2.5</sub>
Total mortality	2,732	1.14 (1.06-1.23)	1.14 (1.06-1.22)
Cardiorespiratory	1,196	1.26 (1.12-1.41)	1.22 (1.11-1.35)
Respiratory	195	1.07 (0.79-1.45)	1.13 (0.84-1.50)
Lung Cancer	226	1.26 (0.96-1.65)	1.26 (0.99-1.61)
Other	1,115	1.02 (0.91-1.16)	1.01 (0.91-1.13)

Rates have been adjusted for age in one-year categories, gender, current smoker, current pack-years of smoking, former smoker, former pack-years of smoking, less than high school education, and a linear and quadratic term for body mass index. Lung cancer (ICD-9 code 162) Cardiovascular disease (ICD-9 codes 400-440); Nonmalignant respiratory disease (codes 485-496)  
<sup>1</sup>Average PM<sub>2.5</sub> calculated as the average of all available sampling data - Six Cities Monitoring Data for years 1979-1985; PM<sub>2.5</sub> estimated from AIRS data for years 1986-1996.



## Future Directions

The contributions of individual source categories (e.g., suspended sulfates from coal combustion, residual oil combustion effluent, resuspended soil, motor vehicle traffic) to total and by-cause annual mortality is being studied using source apportionment techniques and PM compositional analyses based on EPA's Speciation Site network for communities throughout the U.S. having different PM compositional mixtures. (**Figure 5**)

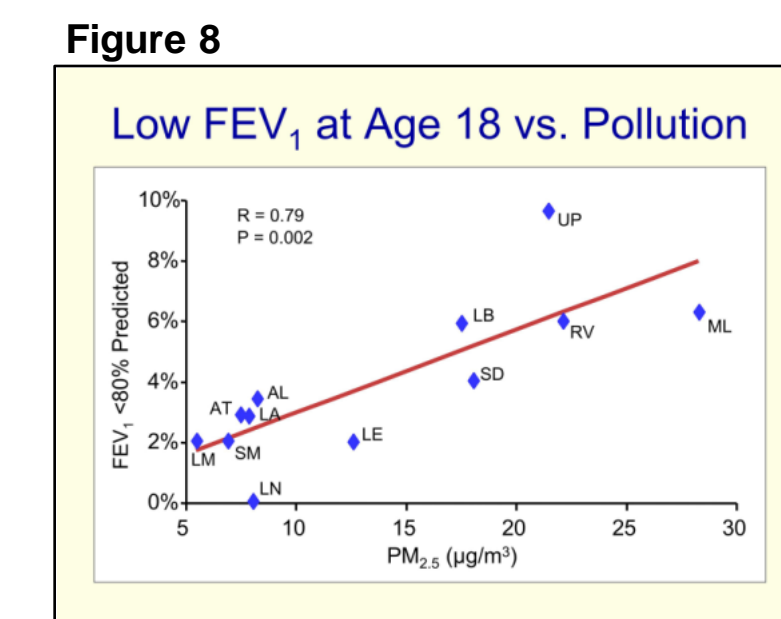
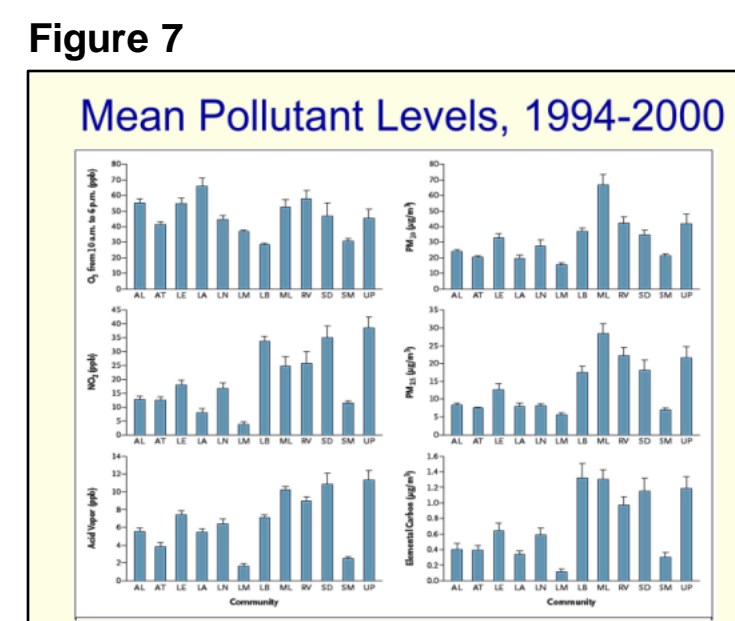
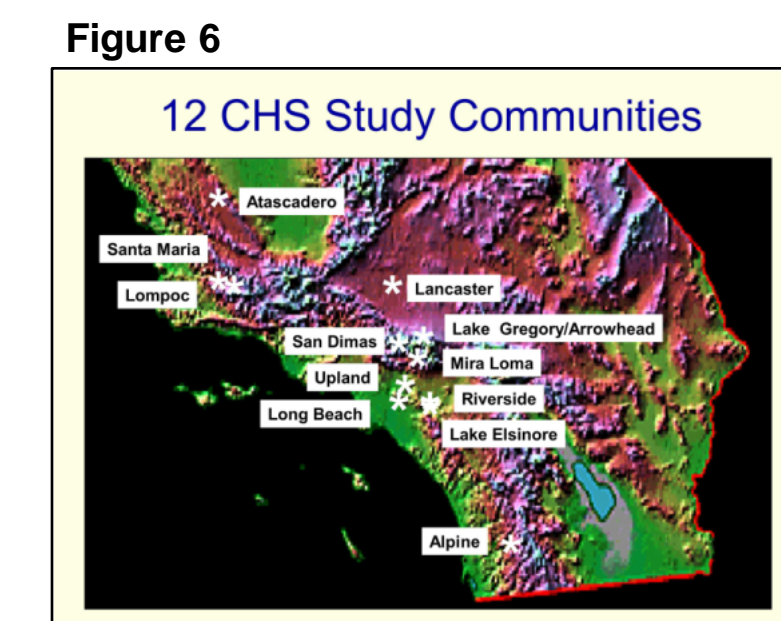
## CHILDREN'S COHORTS

### KNOWLEDGE IN 1997:

A cross-sectional study in 24 U.S. and Canadian cities showed that long-term exposure to PM<sub>2.5</sub> and strongly acidic aerosol was associated with respiratory function deficits, symptoms and illness.

### KNOWLEDGE GAINED SINCE 1997:

In the Children's Health Study (CHS) in 12 Southern California communities, (**Figure 6 and 7**) supported by the California Air Resources Board with supplementary EPA support, and with current support from NIEHS, a cohort of 4<sup>th</sup> graders were studied annually until high school graduation. Among the many findings from this multidimensional study are: 1) lung function growth in a 4<sup>th</sup> grade cohort was significantly lower in proportion to the concentrations of PM<sub>2.5</sub>, NO<sub>2</sub>, and acid vapors (**Figure 8**); 2) children who moved, during the study, from lower pollution communities to more polluted communities had slower lung function growth than those that stayed, and those moving from dirtier communities to less polluted communities had greater lung growth than those that stayed; and 3) analyses of the role of within-community variations in traffic-related air pollution (supported by EPA) showed that proximity to high traffic density roads is associated with asthma onset, asthma-related school absence, and impaired lung function growth, and that particulate organic carbon is associated with bronchitis among asthmatic children.



**CHS – EPA Supplement- Health Effects of Motor Vehicle Emissions**

Proximity of residence to high traffic density is significantly associated with:

- asthma onset,
- asthma-related school absence,
- reduced lung function growth, and that

Organic carbon within the PM<sub>2.5</sub> is associated with:

- bronchitis among asthmatic children.

### Conclusions

- NO<sub>2</sub>, PM<sub>2.5</sub>, elemental carbon, and acid vapor associated with deficits in 8-yr growth
- All children at risk, not just susceptible subgroups
- Deficits in 8-yr growth resulted in clinically significant deficits in FEV<sub>1</sub> at age 18
- Reduced lung function is likely to persist through adulthood

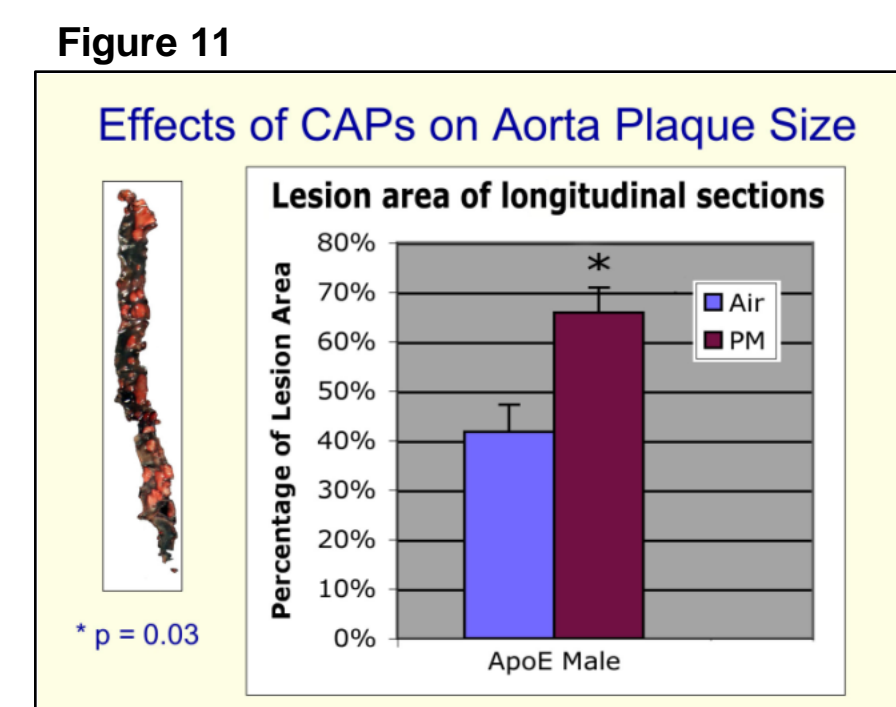
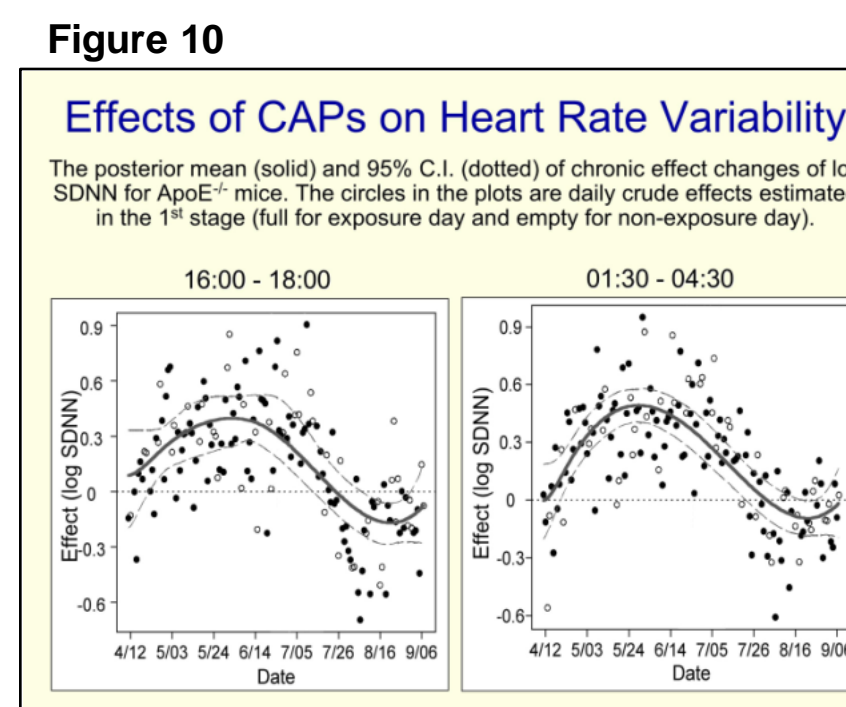
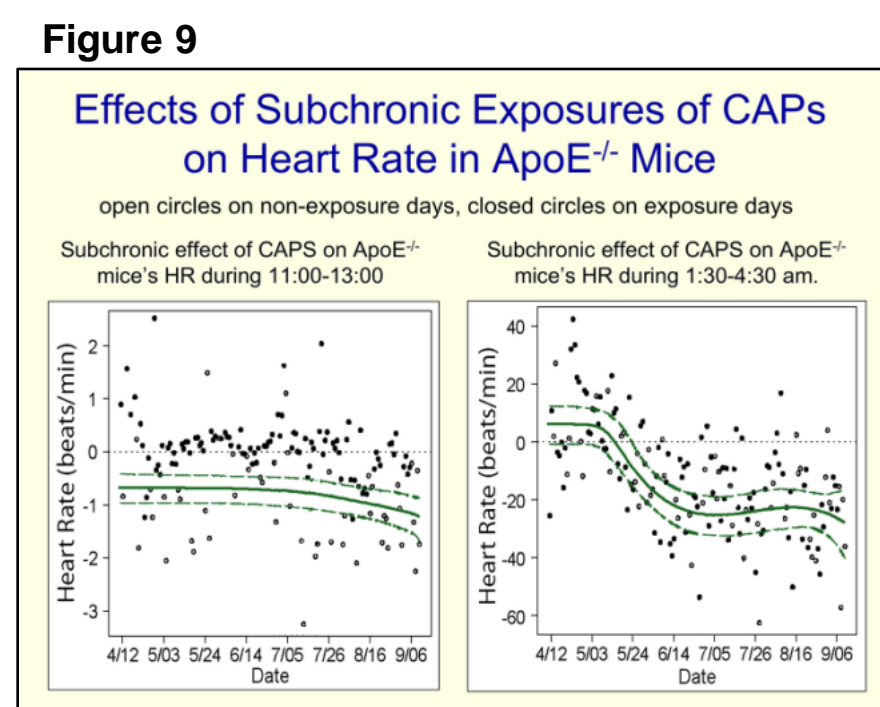
## Future Directions

With EPA and NIEHS support, further research on the CHS cohorts will focus on: 1) a new cohort of kids looking for incident and prevalent asthma related to regional and local (traffic) pollution; 2) studies of exhaled NO as a predictor of air pollution effects (both oxidative and nitrosative); 3) genetic influences on susceptibility to pollution; and 4) studies of intracommunity variability of pollutants and their effects.

## SUBCHRONIC ANIMAL STUDIES

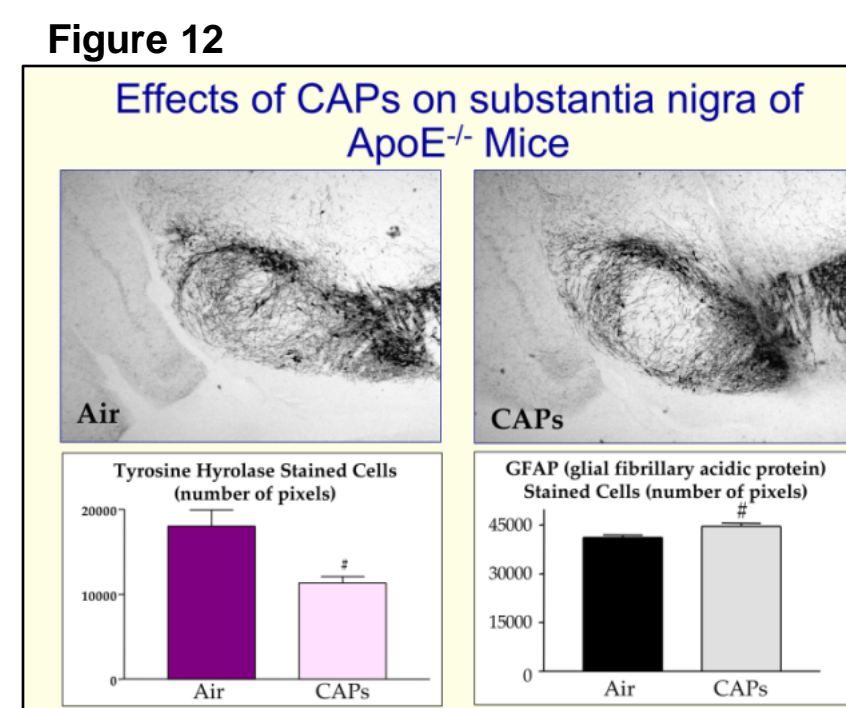
### KNOWLEDGE GAINED SINCE 1997:

The biological plausibility for cumulative effects of chronic exposure to ambient air PM<sub>2.5</sub> has been enhanced by the results of a subchronic inhalation exposure study of mice. Normal mice (C57) and a murine model of atherosclerotic disease (ApoE<sup>-/-</sup>) were exposed for 6 hr/day, 5 days/wk for 5 months in the summer of 2003 to Tuxedo, NY (ambient northeastern regional PM<sub>2.5</sub> background) aerosol that was inertially concentrated ten-fold (av. Conc. = 110 µg/m³). There were no significant exposure-related effects in the C57 mice. However, in the ApoE<sup>-/-</sup> mice, there were both short-term and cumulative effects on heart rate (HR) and heart rate variability (HRV) (**Figures 9 & 10**). At the end of the exposures, there were significant differences between PM<sub>2.5</sub> exposed and sham-exposed mice in aortic plaque density and invasiveness (**Figure 11**), expression of genetic markers for circadian rhythm, and cell density in the substantia nigra in the brain (**Figure 12**). Source apportionment analyses were applied to the short-term changes in HR and HRV, and each of the four source categories (secondary sulfate, resuspended soil, residual oil combustion, and motor traffic) was associated with a different transient change in HR or HRV (**Table II**).



**Assessing Effects of CAPs on Gene Expression Levels in Lung and Heart**

- Used Affymetrix GeneChips
- 3 animals/strain/exposure group/tissue
- Heart genes altered by subchronic CAPs exposure
  - Pyruvate dehydrogenase kinase - Energy regulation
  - 6 ion channels for K<sup>+</sup>, Na<sup>+</sup>, and Ca<sup>2+</sup> - Ion balance
  - Myosin heavy chain - muscle
  - Albumin D-element binding protein - Circadian rhythm
  - Heat shock proteins - Protection from injury



**Summary of the First Subchronic CAPs Exposure Study**

- Subchronic exposure to CAPs produced cumulative changes in body core temperature, heart rate, and heart rate variability.
- Animals prone to develop atherosclerosis were more sensitive to CAPs exposure than normal mice.
- Subchronic CAPs exposure markedly accelerated plaque development and affected plaque characteristics.
- Subchronic CAPs exposure produced alterations in the brain that are consistent with Parkinson's disease.
- Subchronic CAPs exposure produced alterations in gene expression in heart and lung tissues.

**Table 2**

Short-Term Cardiac Function Changes in ApoE<sup>-/-</sup> Mice Associated with PM Components with Significant p-Values

PM Component	Time of day	Affected Variable	10 <sup>-3</sup> x Effect coefficient	p	Conc. µg/m³			Interquartile Change
					mean	first quartile	third quartile	
PM2.5	11:00-13:00	HR	-47.67	0.00	113.0	55.21	141.48	-4.1 bpm
Resuspended Soil	11:00-13:00	HR	361.23	0.01	13.18	5.88	18.36	-4.5 bpm
Resuspended Soil	16:00-18:00	HR	209.46	0.05	13.18	5.88	18.36	+2.6 bpm
Secondary Sulfate	16:00-18:00	HR	-36.30	0.05	63.41	25.08	79.20	-2.5 bpm
Residual Oil	16:00-18:00	RMSDD	26.37	0.00	1.53	0.01	2.30	+6.2 %
Secondary Sulfate	1:30-4:30	RMSDD	-1.07	0.00	63.41	25.08	79.20	-5.6 %
Resuspended Soil	1:30-4:30	RMSDD	3.40	0.02	13.18	5.88	18.36	+4.3 %
PM2.5	1:30-4:30	RMSDD	-0.29	0.03	113.0	55.21	141.48	-2.4 %

## Future Directions

The results of follow-on studies in the winter of 2003-2004, and the summer through winter of 2004, incorporating more biological effects assays, are currently being analyzed. Future studies will include simultaneous studies in Tuxedo, NY and New York City to determine the role of the incremental carbonaceous aerosol present in New York City, and will utilize periodic ultrasound imaging to measure aortic plaque growth and its influence on aortic hemodynamics (**Figure 13**). Other studies will be conducted in locations having different PM compositions. These, and studies that enhance the surface concentrations of possibly causal components, or add CO or O<sub>3</sub> to the mixture, will help in identifying the most influential of the components of ambient air pollution.